Exhibit F

Vaginal Mesh Contraction

Definition, Clinical Presentation, and Management

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OBJECTIVE: While transvaginal polypropylene mesh is increasingly used in the management of pelvic organ prolapse, contraction of the mesh after implantation may cause substantial morbidity. This report defines the clinical entity of vaginal mesh contraction.

METHODS: This is a case series of women who underwent surgical intervention for the management of symptomatic vaginal mesh contraction in our tertiary referral urogynecology center between January 2007 and December 2008. We evaluated the presenting symptoms, examination findings, subsequent management, and outcome.

RESULTS: Seventeen women with vaginal mesh contraction were included in this series. Clinical presentation included severe vaginal pain, aggravated by movement (17 of 17), dyspareunia in all sexually active women (14 of 14), and focal tenderness over contracted portions of the mesh on vaginal examination (17 of 17), commonly involving the lateral fixation arms. Mesh erosion (9 of 17), vaginal tightness (7 of 17), and shortening (5 of 17) were frequently present. Surgical intervention consisted of mobilization of the mesh from the underlying tissue, division of fixation arms from the central graft, and excision of contracted mesh. After surgery, 88% (15 of 17; 95% confidence interval 73–104) of women have experienced substantial reduction in vaginal pain and 64% (9 of 14; 95% confidence interval 39–89) experienced substantial reduction in dyspareunia. Three women required subsequent excision of the entire accessible mesh because of persisting symptoms.

CONCLUSION: Vaginal mesh contraction is a serious complication after prolapse repair with armed polypropylene mesh that is associated with substantial morbidity, frequently requiring surgical intervention. Research and development is urgently needed for newer graft materials with diminished shrinkage properties.

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High failure rates after conventional surgeries for pelvic organ prolapse (POP) have led to the introduction of graft materials to the field of pelvic floor reconstruction, aiming to reinforce the native tissues and achieve improved functional and anatomical outcomes. While recent randomized controlled trials have demonstrated that synthetic mesh at the anterior vaginal compartment reduces the risk of prolapse recurrence as compared with anterior colporrhaphy at 1 and 2 years,[1–4] there is no level I evidence to support the use of vaginal polypropylene mesh for apical or posterior compartment prolapse.[5] Commercial polypropylene repair kits are available and typically consist of a prestyled mesh graft with fixation arms that travel through the obturator foramen for anterior compartment reinforcement or through the ischiorectal fossa for the posterior and apical compartments. More recently device related complications have been reported,[6–9] and in October 2008 the U. S. Food and Drug Administration (FDA) published a special notification titled "Serious complications associated with transvaginal placement of surgical mesh in repair of pelvic organ prolapse and stress urinary incontinence." In this release, the U. S. Food and Drug Administration describes more than 1,000 reports from manufacturers of mesh and mesh-based kits of complications associated with these products. The most frequently reported complications included mesh erosion through the vaginal epithelium, infection, pain, urinary problems, and recurrence of prolapse and/or incontinence. A few months before that, Ridgeway et al (Ridgeway B, Walters

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MD, Paraiso MF, Barber MD, McAchran SE, Goldman HB, et al. Early experience with mesh excision for adverse outcomes after transvaginal mesh placement using prolapse kits. Presented at the 34th Annual Scientific Meeting of the Society of Gynecologic Surgeons, April 2008, Savannah, GA) reported their early experience with mesh excision for a variety of adverse outcomes.

While in vivo shrinkage of polypropylene mesh up to 50% of its original size has been previously demonstrated both in animal models[10] and in women,[11] the clinical implication of this biomechanical characteristic remains undefined. During the last 2 years a number of patients who developed substantial morbidity related to mesh contraction have been treated in our unit and despite attempts of conservative management the majority required surgical intervention. The aim of this report is to define the clinical entity of vaginal mesh contraction.

MATERIALS AND METHODS

This case series describes the presenting symptoms, examination findings, subsequent management, and outcome of women who underwent surgical intervention for the management of vaginal mesh contraction after prolapse repair with armed polypropylene mesh kits. The study was approved by the Institutional Review Board at the Royal Brisbane & Women's Hospital. Consecutive women who underwent surgery for symptomatic mesh contraction between January 2007 and December 2008 were included in this series. Women with other mesh-related complications (erosion, infection, etc) without associated contraction were excluded. The medical records of all patients were reviewed by the principal author (B.F.), a urogynecology fellow, and relevant information collected including demographics, medical and obstetric history, previous surgeries, presenting symptoms and examination findings, details of conservative and/or surgical management, and outcome. The clinical evaluation consisted of abdominal palpation, speculum visualization of the vagina including prolapse quantification using the International Continence Society POP-Q system,[12] and bimanual vaginal and rectal examination. On bimanual examination the clinician carefully palpated all areas of the vaginal epithelium. Any abnormal findings such as focal or diffuse tenderness, increased mesh tension, or the presence of prominent bands under the vaginal mucosa were recorded. Descriptive statistical calculations including means, medians and standard deviations were used for demographic parameters and 95% confidence intervals (CIs) were calculated as part of the outcome analysis of the surgical interventions.

To identify previous publications on this entity we searched the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews and Effects, American College of Physicians Journal Club and MEDLINE (1950 to June 2009) using the terms "vaginal mesh contraction," "mesh complications," and "mesh shrinkage." No language limitations were used. We also hand-searched conference proceedings of the International Urogynecological Association, the International Continence Society, the American Urogynecologic Society, and Society for Gynecologic Surgeons between January 2007 and June 2009.

All women initially underwent a variety of conservative management including topical estrogen therapy, pelvic floor muscle exercises, and vaginal dilators. Women with persisting symptoms underwent surgical intervention. All surgeries were performed by the two authors of this manuscript, ie, a consultant urogynecologist and a urogynecology fellow, in operating theater setting with the patient under general anesthesia.

An examination with the patient under anesthesia is performed, and the areas of contracted mesh, including any involved mesh arms, are identified by palpation. The vaginal epithelium covering the mesh is infiltrated using 0.25% bupivacaine with 1:400,000 adrenalin for hydrodissection and hemostasis. The vaginal epithelium is incised with a scalpel and dissected off the underlying tissue using sharp dissection with Metzenbaum scissors. The mesh is identified and grasped with Moynihan forceps. With counter-traction applied by the forceps, the mesh is gently dissected off the bladder or rectum using scissors. The plane of dissection has to be parallel to the mesh, and the tips of the scissors should point away from the underlying viscus to avoid inadvertent injury. When dissecting laterally to mobilize contracted mesh arms, medial traction of the mesh is valuable to improve visualization and access. The mesh arms should be transected as lateral as possible, and any contracted areas of mesh should be excised. Not uncommonly the mesh is firmly adhered to the fascia and cannot be safely removed in one step. In these cases it should be mobilized and removed in a piecemeal fashion. It is typically more difficult to define the extent of the contracted mesh once the vaginal epithelium has been incised and dissected. Therefore it is highly important to determine the affected area before the first incision. The same surgical principles apply in cases in which removal of the entire mesh is indicated due to failure of a previous partial excision to alleviate

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symptoms. In these cases, the central body of the mesh and the arms medial to the pubic rami at the anterior compartment and to the sacrospinous ligament at the apical compartment are excised. After satisfactory hemostasis is obtained, the vaginal epithelium is approximated using 2/0 Polyglactin absorbable suture (Vicryl, Ethicon, Somerville, NJ). In cases of concomitant mesh erosion, distal from the site of contraction, the surrounding vaginal epithelium is mobilized from the underlying mesh using sharp dissection, and the eroded mesh is grasped with Moynihan forceps and excised until no mesh is visible or palpable underneath the epithelial edges. The vaginal epithelium is then oversewn. At the end, cystoscopy and rectal examination are performed to ensure bladder and rectal integrity, the vagina is packed, and an indwelling urethral catheter is inserted overnight.

RESULTS

Seventeen women were included in this review. Ten of these women (60%) underwent the initial mesh repair in different institutions and were referred to our tertiary referral center for the management of their adverse postoperative outcome. Seven were originally operated on by our team and are included in an ongoing analysis to be published in the future, which will help estimate the incidence of this complication.

Demographics and surgical history are detailed in Table 1. All women had previously undergone armed polypropylene mesh reconstructive surgery, and in 65% of women (11 of 17) this was the primary intervention for POP. None of the patients underwent further interventions between the mesh implantation and presenting to our unit. In all cases the type of mesh kit used for prolapse repair was either anterior mesh alone or combined anterior and posterior mesh kits. The Total Prolift system (Ethicon Women's Health and Urology, Somerville, NJ) was used in six women (35%), Anterior Prolift and Perigee (American Medical Systems Inc., Minnetonka, MN) systems were used in four patients (24%) each, and Apogee–Perigee in conjunction was used in three women (18%). All included patients failed to respond to conservative management and required at least one surgical intervention. The median (range) time from mesh implantation to seeking medical care for symptomatic mesh contraction was 20 (4–52) weeks.

The presenting symptoms and examination findings are detailed in Table 2 and demonstrate that 100% of women had severe vaginal pain, which was aggravated by movement, and all sexually active women experienced severe dyspareunia. On vaginal examination all women had prominent tense focal areas of mesh palpated under the vaginal epithelium. In 82% (14 of 17) of the women the junctions between the fixation arms and the main body of the mesh were the focal site of tension, with the proximal arms of the anterior mesh accounting for 71% (10 of 14) of cases. In all the women palpation of the localized prominent tense mesh under the vaginal mucosa reproduced the pain the patients experience with movement and intercourse.

The extent of surgical intervention performed was proportional to the severity of symptoms and physical findings, and the various procedures are detailed in Table 3. Median (range) postoperative review was 24 (6–84) weeks, and Table 4 presents the clinical outcome of the surgical management. Eighty-eight percent of women (15 of 17, 95% CI 73–104) had resolution of the vaginal pain after the primary surgery, and 64% of sexually active women (9 of 14, 95% CI 39–89) experienced substantial reduction in dyspareunia. Three patients who had persisting symp-

Table 1. Demographics and Surgical History

Variable	
Age [mean y±SD]	54.9±11.7
Parity [median (range)]	2 (1–6)
BMI [mean kg/m^2±SD]	27.6±5.8
Previous hysterectomy [n (%)]	11 (65)
Previous prolapse repair with polypropylene mesh kit [n/N (%)]	17/17 (100)
Prolapse surgery prior to mesh implantation [n/N (%)]	6/17 (35)

SD, standard deviation; BMI, body mass index.

Table 2. Clinical Presentation of Women With Vaginal Mesh Contraction

	n (%) (N=17)
Symptoms	
Severe vaginal pain	17 (100)
Dyspareunia	14 (100*)
Vaginal discharge/spotting	3 (18)
Male discomfort	1 (7*)
Awareness of prolapse	1 (6)
Examination findings	
Focal vaginal tenderness over contracted mesh	17 (100)
Prominent tender band(s) over mesh arm(s)	14 (82)
Vaginal tightness	7 (41)
Foreshortened vagina (TVL less than 7 cm)	5 (29)
Mesh erosion	9 (53)

TVL, total vaginal length.
* Value represents the percent of the sexually active women.

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Table 3. Surgical Procedures

Intervention Arm	n (%)
First intervention (n=17)	
A	3 (18)
B	3 (18)
E	1 (6)
A+C	1 (6)
B+C	2 (12)
B+D	3 (18)
B+C+D	2 (12)
C+D	2 (12)
Second intervention (n=3)	
E	3 (100)

A, mobilization and division of mesh arms (without excision); B, excision of mesh arms; C, partial excision of the central mesh graft; D, management of mesh erosion; E, excision of the entire accessible mesh.

toms with further tense areas of contracted mesh on examination underwent complete excision of the accessible mesh, resulting in substantial reduction in pain. One of the three reported on resolution of the dyspareunia after the intervention, and two had not been sexually active yet at the time of the review. One woman presented with multiple mesh erosions and a multifocal contraction after a Perigee mesh implantation, and therefore the entire mesh was excised at the first surgical intervention. Another woman who underwent complete excision of the mesh subsequently presented with a recurrent symptomatic vault and anterior vaginal prolapse, and a laparoscopic sacralcolpopexy and paravaginal repair were performed at a later stage.

In summary, in our review all women presented after undergoing prolapse repair with transvaginal armed polypropylene mesh and experienced severe vaginal pain and dyspareunia (those who were sexually active) subsequently. On a thorough vaginal examination localized areas of prominent tense mesh were noticed under the vaginal epithelium in all the patients. Palpation of the contracted mesh reproduced the pain these women experienced with movement and sexual intercourse. After primary surgical intervention to release the tension caused by the contracted mesh, 88% of patients had resolution or substantial reduction of the vaginal pain. All women had resolution of the pain if including the three who underwent further excision of the entire accessible mesh.

Table 4. Outcome After Surgical Intervention

Outcome	Proportion of Women (%)
Outcome after first intervention	
Substantial reduction in vaginal pain	15/17 (88)
Substantial reduction in dyspareunia	9/14 (64)
Sexual discomfort due to foreshortened vagina	1/14 (7)
Minor improvement only/no change	2/17 (12)
Outcome after second intervention	
Substantial reduction in vaginal pain	2/2 (100)
Substantial reduction in dyspareunia	1/3 (33)
Not sexually active yet	2/3 (66)

After evaluating the presenting symptoms, examination findings, and outcome analysis we define vaginal mesh contraction as an adverse outcome after prolapse repair with armed polypropylene mesh in women who experience vaginal pain with movement and dyspareunia and on examination have localized areas of prominent tense and tender mesh under the vaginal epithelium.

DISCUSSION

In this report we describe the clinical presentation, surgical management, and outcome of women with vaginal mesh contraction after pelvic organ prolapse repair with armed polypropylene mesh kits. The main clinical features include severe vaginal pain with movement, dyspareunia, and focal tenderness over contracted portions of the mesh on vaginal examination. This is the first article to define the clinical entity of vaginal mesh contraction as well as the largest series written on this adverse surgical outcome as confirmed by our thorough literature search, in which we were unable to locate any series defining or relating to the clinical implication of this entity.

Although shrinkage of synthetic mesh after implantation had been reported by Amid et al[13] as early as in 1997, the etiology of this phenomenon is still unknown, and different theories have been suggested. García-Ureña et al[10] considered graft shrinkage to be a physical consequence of the inflammatory response to the mesh, while Gonzalez et al[14] argued that it is a result of inadequate tissue ingrowth into the mesh. While the pathophysiology remains unclear, there is growing evidence to suggest that synthetic mesh shrink significantly once incorporated in the biological tissues. This evidence emerges both from animal studies, in which the rate of shrinkage can be directly assessed by comparing the graft's area preoperatively and postoperatively,[10] and from human studies involving mesh for hernia or prolapse repair.[11] Using imaging techniques such as ultrasonography or magnetic resonance imaging, the dimensions of the graft can be assessed postoperatively and compared with those of the original mesh. More recently Letouzey et al (Letouzey V, Deffieux X, Levaillant J, Faivre E, de Tayrac R, Fernandez H. Ultrasound evaluation of

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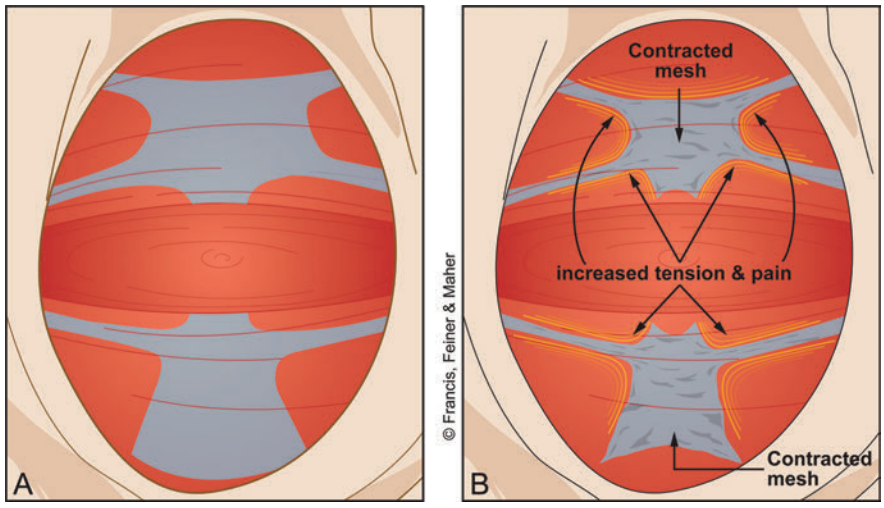

Fig. 1. Illustration of anterior and posterior vaginal mesh layout, showing an anterior mesh with four arms above and a posterior mesh with two apical arms below: at implantation **(A)** and after the body of the mesh has contracted by 30% **(B)**. Increased tension is demonstrated by the narrowing of the arms, and areas of pain are demonstrated by curved lines. Illustration: Stephen Francis. Copyright ©2009, Francis, Feiner, and Maher.

Feiner. Vaginal Mesh Contraction. Obstet Gynecol 2010.

polypropylene mesh contraction at long term after vaginal surgery for cystocele repair. Presented at the 34th Annual Scientific Meeting of the International Urogynecological Association, June 2009, Lake Como, Italy) reviewed the long-term changes in mesh volumes over time using three-dimensional translabial ultrasonography and found mean contraction of 30%, 65%, 85% at follow-up durations of 3, 6, and 8 years, respectively. This study demonstrates that the pathological process that causes mesh shrinkage is progressive and there is a linear evolution of the contraction rate with time, raising the worrying possibility that mesh contraction syndrome that we have defined may be encountered more frequently in the future.

The present study however focuses on the clinical expression of mesh contraction rather than on the biomechanical phenomenon. All of the women included in this series had a clearly palpable painful mesh contraction that brought them to seek medical care. In the majority of cases the most severe tenderness on vaginal examination was present at the junctions between the central mesh graft and the fixation arms as a result of excessive tension after shrinkage of the main body of the mesh against the serrated arms that remain fixated and unmovable in the tissue (Fig. 1). This tension is also likely to be responsible for the extremely high erosion rate (53%) seen in this group of patients as compared with published data on polypropylene mesh erosion rates after prolapse repair (5–20%).[2,15] An alternative explanation for the pathophysiology of this scenario can be either excessive tensioning of the arms or bunching of the mesh at implantation. The manufacturer's instructions and mentoring programs all stress the importance of a tension-free insertion of the mesh as a flat sheet without bunching. The use of vaginal pack postoperatively is nearly universal and further acts to reduce the likelihood of both bunching of the graft and excessive tension on the fixation mesh arms.

The goal of our surgical management was to relieve the tension by dividing the central graft from the arms and excising all areas of mesh contraction. This approach led to a substantial reduction in the vaginal pain in 88% of women and in dyspareunia in 64% after the primary intervention. Further improvement was reported by women who underwent a subsequent removal of the entire accessible mesh. This surgical intervention however is potentially associated with an increased risk of visceral injury and hemorrhage as the tissue is often firmly adhered to the mesh and surgical planes rarely exist. Moreover, re-approximation of the vaginal epithelium after excision of the mesh is often challenging as the vaginal tissue itself is typically scarred and fragile in areas of mesh contraction.

The retrospective nature of this study is associated with possible weaknesses, including failure to adequately document pre–mesh insertion morbidity, which is exacerbated by the fact that 60% of the patients had their initial interventions performed in other institutions, where variability in indications for surgery and in surgical techniques exist. A further weakness is the inability to estimate the incidence of symptomatic mesh contraction as opposed to asymptomatic shrinkage. Finally, three-dimensional ultrasound assessment of mesh volumes would have been beneficial, although not essential, in the context of defining the clinical implication of a biomechanical

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phenomenon that has been well documented in previous work.

Vaginal mesh contraction is a serious complication after pelvic organ prolapse repair using armed polypropylene mesh. It is characterized by severe vaginal pain and dyspareunia and on vaginal examination focal tenderness over contracted portions of the mesh. Surgical intervention is often required to alleviate symptoms. It involves mobilization of the mesh, division of the fixation arms, and excision of contracted mesh. Removal of the mesh en-block is reserved, as a last resort, for the most severe and persistent cases. Longer follow-up is required to estimate the outcome after the surgical management, and profound research and development effort is urgently needed for newer graft materials with diminished shrinkage properties.

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